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(71) Applicant (*for all designated States except US*): ROCHE DIAGNOSTICS GMBH [DE/DE]; Sandhofer Strasse 116, D–68305 Mannheim (DE).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): KRELL, Hans–Willi [AT/DE]; Zugspitzstrasse 14a, D–82377 Penzberg (DE). GRAMS, Frank [DE/DE]; In den Alten Wiesen 55, D–68219 Mannheim (DE). BRUNNER, Alfred [DE/DE]; Kirnbergwiese 18, D–82393 Iffeldorf (DE).

(74) Common Representative: ROCHE DIAGNOSTICS GMBH; Sandhofer Strass 116, D–68305 Mannheim (DE).

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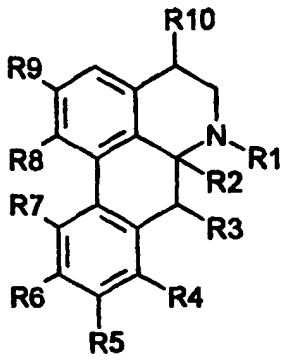
(54) Title: APORPHINOID MATRIX METALLOPROTEINASE INHIBITORS

(57) Abstract

Use of a compound of formula (I) wherein R1 represents hydrogen, hydroxy, acyl, halogenyl or C1–C6–alkyl; R2 represents hydrogen, hydroxy, halogenyl, cyano, C1–C6–alkyl, or acyl; R3 and R4 represent independently of each other hydrogen, hydroxy, halogenyl, C1–C7–alkyl, acyl or a monocycle; R5, and R6 represent independently of each other hydrogen, hydroxy, mercapto, C1–C8–alkyl, C1–C7–alkoxy or acyl; R7 represents hydrogen, hydroxy, halogenyl or amino; R8 represents hydrogen, hydroxy, mercapto, C1–C8–alkyl, acyl or R8 and R9 represent together O–(CH2)n–O with n equals 1 or 2; R9 represents hydroxy, mercapto, C1–C7–alkoxy or C1–C7–alkylthio; R10 represents hydrogen, hydroxy, mercapto, halogenyl or amino, C1–C16–alkyl, acyl, an optionally substituted mono– or bicyclus; and pharmacologically acceptable salts or prodrugs thereof, to produce pharmaceutical agents for the treatment of diseases where MMP activity is involved, processes for their production and pharmaceutical agents which contain these compounds having a matrix metalloprotease–inhibitory action.



(I)

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EX. 30-W, page 13-14

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APORPHINOID MATRIX METALLOPROTEINASE INHIBITORS

In normal tissue there is an equilibrium between synthesis and degradation. Extracellular matrix is degraded by proteases which belong to at least three groups of matrix metalloproteases. These are the collagenases, gelatinases and stromelysins. Normally there are endogenic inhibitors for these catabolic enzymes such as α_2 macroglobulines and TIMP (= tissue inhibitor of metalloproteases (MMP)) so that an excessive degradation of extracellular matrix does not occur.

At least 15 different and yet highly homologous MMP species have been characterized, including the interstitial fibroblast collagenase (MMP-1, HFC), the neutrophil collagenase (MMP-8, HNC), two gelatinases (gelatinase A or MMP-2 and gelatinase B or MMP-9), stromelysins (such as HSL-1, MMP-3) and Matrilysin (MMP-7). These proteinases share a number of structural and functional features but differ somewhat in their substrate specificity. Only HNC and HFC are capable of cleaving type I, II and III native triple-helical collagens at a single bond with the production of fragments 3/4 and 1/4 of the native chain length. This lowers the collagen melting point and makes them accessible to further attack by other matrix degrading enzymes.

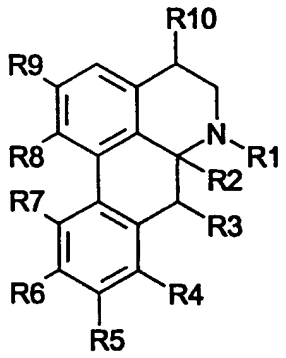
However, the uncontrolled excessive degradation of this matrix is a characteristic of many pathological states such as e.g. in the clinical picture of angiogenesis, tumor progression, sun-induced skin-aging, emphysema, cardiovascular diseases like restinosis, arteriosclerosis and platelet aggregation, rheumatoid arthritis, osteoarthritis, periodontal diseases, multiple sclerosis, in the formation of tumour metastases, corneal ulceration, inflamative diseases and diseases, where the presence of bacteria results in the release of MMPs, like bacterial Meningitis.

It can be assumed that the pathogenesis of these clinical pictures can be favourably influenced by the administration of matrix metalloprotease inhibitors. A number of compounds are known in the literature (see e.g. the review article of Beckett RP, Davidson AH, Drummond AH, Huxley P, Whittaker M. Drug Disc. T. (1996)1: 16-26.)) or are described in the patent literature, these mainly being peptides with a hydroxamic acid residue, a thiol or phosphinic group as a zinc binding group (see e.g. WO-A-9209563 by Glycomed, EP-A-497 192 by Hoffmann-LaRoche, WO-A-9005719 by British Biotechnology, EP-A-489 577 by Celltech, EP-A-320 118 by Beecham, US-A-459 5700 by Searle among others).

Some of these compounds have a high activity as inhibitors of matrix metalloproteases but only have a very low oral availability.

It has now been found that the claimed Aporphinoidderivatives are very efficacious as matrix metalloprotease inhibitors and are orally availability.

The present invention therefore concerns the use of substances of the general formula I



wherein

R1 represents hydrogen, hydroxy, acyl, halogenyl or C1-C6-alkyl;

R2 represents hydrogen, hydroxy, halogenyl, cyano, C1-C6-alkyl, or acyl;

R3 and R4 represent independently of each other hydrogen, hydroxy, halogenyl, C1-C7-alkyl, acyl or a monocycle;

R5, and R6 represent independently of each other hydrogen, hydroxy, mercapto, C1-C8-alkyl, C1-C7-alkoxy or acyl;

R7 represents hydrogen, hydroxy, halogenyl or amino;

R8 represents hydrogen, hydroxy, mercapto, C1-C8-alkyl, acyl or R8 and R9 represent together O-(CH2)n-O with n equals 1 or 2;

R9 represents hydroxy, mercapto, C1-C7-alkoxy or C1-C7-alkylthio.

R10 represents hydrogen, hydroxy, mercapto, halogenyl or amino, C1-C16-alkyl, acyl, a optionally sustituted mono- or bicyclus;

and pharmacologically acceptable salts or prodrugs thereof,

to produce pharmaceutical agents for the treatment of diseases where MMP activity is envolved.

Preferred is the use of substances of the general formula I to produce pharmaceutical agents for the treatment of diseases where MMP activity is envolved, with the proviso that alkyl represents a saturated carbo-chain wherein

R1 represents hydrogen, hydroxy, acyl, C1-C5-alkoxy, C1-C5-alkenoxy, halogenyl or C1-C5-alkyl or C1-C5-alkenyl;

R2 represents hydrogen, hydroxy, halogenyl, cyano, C1-C5-alkyl, C1-C5-alkenyl, C1-C5-alkenoxy or C1-C5-alkoxy, acyl;

R3 and R4 represent independently of each other hydrogen, hydroxy, halogenyl, C1-C7-alkyl, C1-C7-alkenyl, acyl or a monocycle;

R5, and R6 represent independently of each other hydrogen, hydroxy, mercapto, C1-C7-alkyl, C1-C7-alkoxy, acyl, or C1-C7-alkylthio, C1-C7-alkenyl, C1-C7-alkenoxy, or C1-C7-alkenylthio;

R7 represents hydrogen, hydroxy, halogenyl or amino;

R8 represents hydrogen, hydroxy, mercapto, C1-C7-alkyl, C1-C7-alkoxy, C1-C7-alkylthio, C1-C7-alkenyl, C1-C7-alkenoxy, C1-C7-alkenylthio, acyl or R8 and R9 represent together O-(CH2)n-O with n equals 1 or 2;

R9 represents hydroxy, mercapto, C1-C7-alkoxy or C1-C7-alkylthio.

R10 represents hydrogen, hydroxy, mercapto, halogenyl or amino, C1-C15-alkyl, C1-C15-alkoxy, C1-C15-alkylthio, C1-C15-alkenyl, C1-C15-alkenoxy, C1-C15-alkenylthio, acyl, a optionally sustituted mono- or bicyclus;
and pharmacologically acceptable salts or prodrugs thereof,

R1 is preferably methyl or hydrogen.

R2 is preferably hydrogen.

R3 is preferably hydrogen.

R4 is preferably hydrogen.

R5 is preferably hydroxy, C1-C3-alkoxy, especially methoxy, mercapto, C1-C3-alkylthio, especially methylthio.

R6 is preferably C1-C3-alkoxy, especially methoxy.

R7 is preferably hydroxy or hydrogen.

R8 is preferably hydroxy, C1-C12-alkoxy, mercapto, C1-C12-alkylthio.

R9 is preferrably hydroxy or mercapto.

In addition the invention concerns new substances of the general formula I, whererin R9 represents mercapto or C1-C7-alkylthio. Also new substances of general formula I are such wherein the residues R1 to R10 has the following meanings
R1 represents C2-C5-alkyl or halogenyl;
R2 represents halogenyl, cyano, C2-C5-alkyl, or C2-C5-alkoxy;
R3 represent halogenyl, C1-C7-alkyl or a monocycle

R4 represent halogenyl, C2-C7-alkyl or a monocycle;

R5, R6, R8 and R9 represent independently of each other mercapto, C2-C7-alkyl, C2-C7-alkoxy, or C1-C7-alkylthio;

R7 represents halogenyl or amino;

R10 represents mercapto, halogenyl or amino, C1-C15-alkyl, C1-C15-alkoxy, C1-C15-alkylthio, a optionally sustituted mono- or bicyclus;

and pharmacologically acceptable salts or prodrugs thereof,and pharmacologically acceptable salts or prodrugs thereof.

Within the scope of the general formula I many aporphine alkaloids are known. A selection is: Aporphine, Boldine, Apomorphine, Laurotetanine, Norisocorydine, Isocorydine, Glaucine, Nuciferine, Fissoldine, Norglaucin, Xylpine, Actinodaphnine and others like dicentrine. Boldine and Glaucine are well known as ingredients of extracts from Annonaceae, Lauraceae, Magnoliaceae, Monimiaceae and others. Boldine is one of many ingredients of Monimiaceae Peumus boldus, commonly called Boldo. Boldo is used as vermifuge, to treat liver, gall bladder and bowel dysfunctions, or inflammation. Boldine is believed to be responsible for both the choleretic and diuretic activity of the leaves from Boldo. In rat aorta (S)-Boldine depressed contractions evoked by noradrenaline in a concentration dependent manner (Ivorra MD et al. Eur. J. Pharmacol. 231: 165-74 (1993)). Boldine and Glaucine show inhibitory effects on TPA induced down regulation of gap junction function (Hu J et al. Biochem. Pharmacol. 50: 1635-43 (1995) and show antioxidative properties (Pharmacol. Res. 31: 103-7 (1995)). Moreno PRH et al. (Int J. Pharmacog. 31: 189-192 (1993)) show anti-tumor activity using a crude extract of Nectandra grandiflora bark. This extract contains less than 0.5% Boldine. Gonzales-Cabello R. et al. J. Invest. Allergol. Clin. Immunol. 4: 139-145 (1994) show effects of Boldine on cellular immune functions in vitro. It is suggested that the immune and antioxidant properties of boldine induce effects on patients with cancer, autoimmune and other diseases. Boldine has been described as effective inhibitor of the prostaglandin biosynthesis which is involved in the carrageenan induced inflammation in guinea pig (Backhouse et al., Agents Actions 42: 114-117 (1994)).

Boldine and related compounds have been shown as inhibitors of platelet aggregation, however the mechanism is yet unclear (Chen et al., Planta Medica 62, 133-136 (1996)). None of the references cited above show or assume the effect of compounds of the general formula I as inhibitors of Metalloproteases or especially of MMPs. Compounds of the general formula 1 with R9 = thiol or thiolalkyl has not been published at all.

The monocycle listed in the case of R_3 and R_{10} is understood as saturated or unsaturated ring systems with 3 - 8, preferably 5 - 7 carbon atoms which can optionally be interrupted one or several times by heteroatoms such as nitrogen, oxygen or sulphur in particular a cyclopentyl, cyclohexyl, cycloheptyl, morpholinyl, thiamorpholinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, furyl, thiophenyl, imidazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl or 1,2,4-triazolyl residue. Lower alkyl, alkoxy and halogen come above all into consideration as substituents.

The bicycle listed under R_{10} is understood to be a condensed bicycle or a bicycle of the type monocycle$_1$-L-monocycle$_2$, wherein L denotes a valence dash C_1-C_4-alkyl group, C_2-C_4 an alkenyl group, an oxygen or -C(O)-group.

The bicycle is preferably a residue such as a naphthyl, tetrahydronaphthyl, dekalinyl, quinolinyl, isoquinolinyl, tetrahydroquino-linyl, tetrahydroisoquinolinyl, indolyl, benzimidazolyl, indazolyl, oxindolyl, benzofuranyl, benzothiophenyl, benzthiazolyl, benzoxazolyl, purinyl, biphenyl or (4-phenoxy)phenyl residue and in particular a naphthyl, biphenyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, indolyl or benzimidazolyl residue.

The residues listed under R2, R3, R4, R5, R6, R8, R9 R10 can optionally be substituted once or several times by halogen, hydroxy, thio, alkyl, hydroxyalkyl, alkoxy, alkylthio, alkylsulfinyl, alkyl-sulfonyl, amino, alkylamino, dialkylamino, nitro, carboxyl, carboxamido, alkoxy-carbonyl, amino or aminocarbonyl optionally substituted once or

twice by lower alkyl, nitrile, oxo, thiocarboxamido, alkoyxythiocarbonyl, alkmercapto-carbonyl, phosphono, alkylphosphono, dialkylphosphono, alkylsulfonylamido, arylamino, aryl, hetaryl, aryloxy, arylthio, arylsulfinyl, arylsulfonyl or acyl.

In this case the halogen, hydroxy, oxo, thio, alkoxy, alkylthio, amino, aminocarbonyl, carboxyl and acyl groups are preferred.

Lower alkyl denotes C_1-C_6-Alkyl, preferred methyl, ethyl, propyl, isopropyl or tert.-butyl.

Acyl in the residues R_1 denotes for -C(O)-C_1-C_6-alkyl or -C(O)H, preferred for an acetyl group.

If not given differently, the alkyl residues in general formula I can optionally be interrupted once or several time by heteroatoms (O, S, NH). If heteroatoms are present, the first backbone atom is preferrably O or S. Alkyl in general formula I or in combination with alkoxy, alkylthio, arylsulfonyl, alkylsulfonyl, alkylaminocarbonyl, arylaminocarbonyl, alkylamino, alkoxycarbonyl, aryloxycarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl represent a straight-chained, branched, saturated or unsaturated residue such as e.g. a methyl, ethyl, propyl, pentyl, octyl, allyl, propargyl, 2,4-pentadienyl, isopropyl, sec. butyl, 3-methylbutyl, 2-hydroxyhexyl and in particular a methyl, propyl, isopropyl, pentyl, octyl, allyl, 3-methylbutyl, 2-hydroxyhexyl and propargyl residue.

Aryl, also in combination with aryloxy, arylthio, arylsulfonyl, arylaminocarbonyl, aryloxycarbonyl, arylaminothiocarbonyl is understood as a phenyl or naphthyl residue which can optionally be substituted in particular by halogen, lower alkyl or alkoxy.

Halogen is understood as chlorine, bromine, iodine and preferably chlorine.

If compounds of the general formula I contain one or several asymmetric carbon atoms, the optically active compounds of the general formula I are also a subject matter of the present invention.

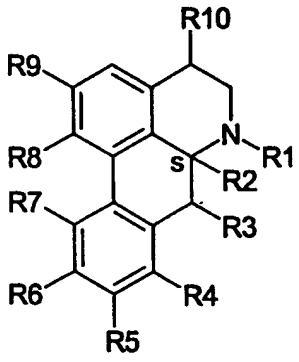
The term "several" means in connection with heteroatoms in monocycles or bicycles preferred one, two or three more preferred one or two, the most preferred heteroatom is nitrogen.

The term "several" means in connection with substituents or substitution preferred one to five, more preferred one, two or three most preferred one or two.

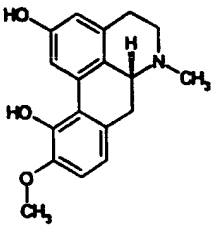
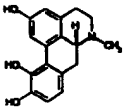
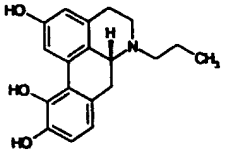
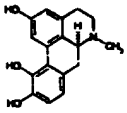
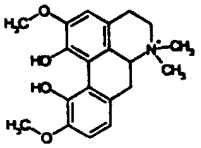
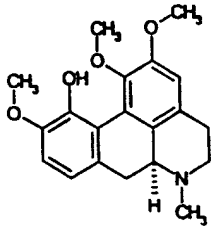
The term "heteroatom" in connection with alkyl or acyl groups means preferred oxygen or NH, more preferred oxygen.

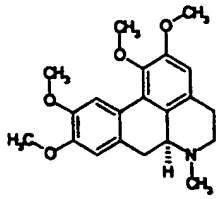
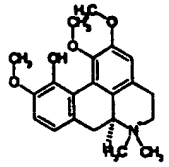
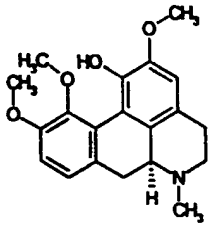
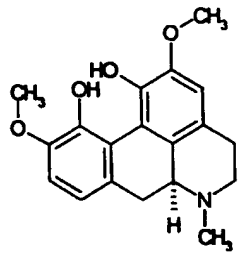
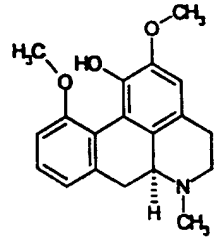
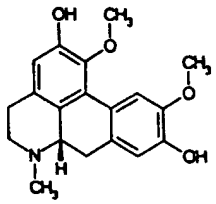
Substitutions of monocycles or bicycles in R_1, R_4 and R_5 are halogen, nitro, hydroxy, alkoxy, amino, alkylamino, dialkylamino, halogenmethyl, dihalogenmethyl, trihalogenmethyl, phosphono, alkylphosphono, dialkylphosphono, SO_2NH_2, SO_2NH(alkyl), SO_2N(alkyl)$_2$, SO_2(alkyl), acetyl, formyl, nitril, COOH, COOalkyl, -OC(O)alkyl, -NHC(O)Oalkyl, OC(O)O-aryl, -NHC(S)NH_2, -NHC(S)NHalkyl, -NHC(O)-aryl.

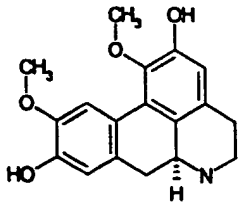
Preferred optical isomers of the compounds of the invention are:

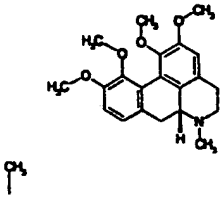


The following compounds are commercially available, can be synthesized or isolated in a manner known in the art:

Example	Structure	Molec. Weight	Name
1		333,813	R(-)-2,11-DIHYDROXY-10-METHOXYAPORPHINE HYDROCHLORIDE
2		364,237	R(-)-2,10,11-TRIHYDROXYAPORPHINE
3		392,290	R(-)-2,10,11-TRIHYDROXY-N-PROPYL-NORAPORPHINE HYDROBROMIDE
4		364,237	S(+)-2,10,11-TRIHYDROXYAPORPHINE HYDROBROMIDE
5		469,312	(+)-MAGNOFLORINE IODIDE
6		341,404	ISOCORYDINE

7		355,431	(+)-GLAUCINE
8		483,339	(+)-MENISPERINE IODIDE
9		341,404	(+)-CORYDINE
10		327,377	(+)-CORYTUBERINE
11		311,378	ISOTHEBAINE
12		327,377	BOLDINE

13  313,351 LAUROLITSINE

14  497,366 O-METHYLISOCORYDINE IODOMETHYLATE

Many other compounds are known from the literature. The following selection provide an illustration of embodiments of the invention and should not be construed to limit the scope of the invention:

Example 15: 6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-1,2-diol

Example 16: 6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-10,11-diol

Example 17: 2-methoxy-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-1,10-diol

Example 18: 2,11-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinolin-1-ol

Example 19: 1,10-dimethoxy-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-2,9-diol

Example 20: 1,2,10-trimethoxy-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinolin-11-ol

Example 21: 10,11-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-1,2-diol

Example 22: 1,10-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-2,11-diol

Example 23: 2,9,10-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinolin-1-ol

Example 24: 1,2,9,10-tetramethoxy-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline

Example 25: 1-(10-hydroxy-1,2-dimethoxy-4,5,6a,7-tetrahydro-dibenzo<de,g>quinolin-6-yl)-ethanone

Example 26: acetic acid 1,2,10-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinolin-9-yl ester

Example 27: 1-(1,2,9,10-tetramethoxy-4,5,6a,7-tetrahydro-dibenzo<de,g>quinolin-6-yl)-ethanone

Example 28: 11-hydroxy-1,2,10-trimethoxy-4,5,6a,7-tetrahydro-dibenzo<de,g>quinoline-6-carbothioic acid phenylamide

Example 29: 10-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-2,11-diol

Compounds of the general formula I can be synthesized by well-known processes preferably in that

a) an alcoholic group of one of the described compounds (in the literature; e.g. Srilankin or Boldin) is converted to an ether using Alkyliodide in basic solution (see Example 30). Reaction products can be isolated by chromatography. In compounds having a phenolic and an alkylic hydroxy group, the phenolic group has to be protected by ester formation first; before the alkylic hydroxy group can be alkylated, since the phenolic hydroxy group is more reactive (e.g. in the case of Srilankin).

b) an alkyl or substitued alkyl or alkenyl or substituted alkenyl group is introduced into one of the bromide substituted compounds described in the literature (e.g. 3,8-Dibromboldin or 3-bromopredicentrine) by protruding protection of the free hydroxy groups by an ester or allyl or benzyl protecting group. After Bromide/Lithium exchange that compound can be reacted with an appropriate (substituted) alkylbromide or (substituted) alkenylbromide by standard procedures. Afterwards the protecting groups can be deprotected. This can be done by standard methods for the ester, with Pd for the allyl and by hydrogenolysis for the benzyl protecting group. Compounds having no bromide group can be bromidated by a standard radical reaction with bromine and the different reactions products can be purified by chromatography, prior to the mentioned alkylation procedure.

c) Compounds with sulfur directly attached to the aporphine sceleton can be obtained from the corresponding oxygen compounds by oxygen/sulfur exchange, which can be done by using O → S exchange reagents, e.g. potassium thiocyanate (e.g. Snyder, H.R., Stewart, J.M., Ziegler, J.B., J. Am. Chem. Soc. (1947) 69, 2672), thiourea (e.g. Ketcham, R., Shah, V.P., J. Org. Chem. (1963) 28, 229), 3-methylbenzothiazole-2-thione (e.g. Calo, V., Lopez, L., Marchese, L., Pesce, G., J. Chem. Soc. Chem. Commun. (1975) 621) and triphenylphosphine sulfide (Chan, T.H., Finkenbine, J.R., J. Am. Chem. Soc. (1972) 94, 2880) or Lowry reagent (Lowry, O.H., Rosebrough, N.J., Faro, A.L., Randall, R.J., JBC (1951) 193, 265-275).

Example 30:

Synthesis of 9-Ethoxy-2-Hydroxy-1-10-dimethoxyaporphine (1,10-dimethoxy-9-ethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-2-ol)

5 nMol of Ethyliodide has been added to a solution of 5 nM 2,9-Dihydroxy-1-10-dimethoxyaporphine and 30 nMol K_2CO_3 in 30 ml Dimethylformamide. After stirring one hour at 50°C the solution was filtered and the solute was evaporated. The product has been purified by chromatography.

The following compounds can be prepared in an analogous manner:

Example 31: 2-Ethoxy-9-Hydroxy-1-10-dimethoxyaporphine (1,10-dimethoxy-2-ethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-9-ol)

Example 32: 2,9-Diethoxy-1-10-dimethoxyaporphine (1,10-dimethoxy-2,9-diethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline)

Example 33: 2-Hydroxy-9-*n*-Propyloxy-1-10-dimethoxyaporphine (1,10-dimethoxy-9-propyloxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-2-ol)

Example 34: 9-Hydroxy-2-*n*-Propyloxy-1-10-dimethoxyaporphine (1,10-dimethoxy-2-propyloxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-9-ol)

Example 35: 2,9-Di-*n*-propyloxy-1-10-dimethoxyaporphine (1,10-dimethoxy-2,9-dipropyloxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline)

Example 36: 2,9-Di-*n*-propyloxy-6a-*n*-propyl-1-10-dimethoxyaporphine (1,10-dimethoxy-2,9-dipropyloxy-6-methyl-6a-propyl-5,6,7-trihydro-4H-dibenzo<de,g>quinoline)

Example 37: 2-*n*-Butyloxy-9-Hydroxy-1-10-dimethoxyaporphine (1,10-dimethoxy-2-butyloxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-9-ol)

Example 38: 2,9-Di-*n*-butyloxy-1-10-dimethoxyaporphine (1,10-dimethoxy-2,9-dibutyloxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline)

Example 39: 9-*n*-Butyloxy-2-Hydroxy-1-10-dimethoxyaporphine (1,10-dimethoxy-9-butyloxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-2-ol)

Example 40: 2,9-Di-*n*-butyloxy-6a-*n*-butyl-1-10-dimethoxyaporphine (1,10-dimethoxy-2,9-dibutyloxy-6-methyl-6a-butyl-5,6,7-trihydro-4H-dibenzo<de,g>quinoline)

Compounds of the general formula I can contain one or several chiral centres and can then be present in a racemic or in an optically active form. The racemates can be separated according to known methods into the enantiomers. Preferably diastereomeric salts which can be separated by crystallization are formed from the racemic mixtures by

reaction with an optically active acid such as e.g. D- or L-tartaric acid, mandelic acid, malic acid, lactic acid or camphorsulfonic acid or with an optically active amine such as e.g. D- or L-α-phenyl-ethylamine, ephedrine, quinidine or cinchonidine.

Alkaline salts, earth alkaline salts like Ca or Mg salts, ammonium salts, acetates or hydrochlorides are mainly used as pharmacologically acceptable salts which are produced in the usual manner e.g. by tritrating the compounds with inorganic or organic bases or inorganic acids such as e.g. sodium hydroxide, potassium hydroxide, aqueous ammonia, C_1-C_4-alkyl-amines such as e.g. triethylamine or hydrochloric acid. The salts are usually purified by reprecipitation from water/acetone.

The new substances of formula I and salts thereof according to the invention can be administered enterally or parenterally in a liquid or solid form. In this connection all the usual forms of administration come into consideration such as for example tablets, capsules, coated tablets, syrups, solutions, suspension etc. Water which contains additives such as stabilizers, solubilizers and buffers that are usual in injection solutions is preferably used as the injection medium.

Such additives are e.g. tartrate and citrate buffer, ethanol, complexing agents (such a ethylenediaminetetra-acetic acid and non-toxic salts thereof), high-molecular polymers (such as liquid polyethylene oxide) to regulate viscosity. Liquid carrier substances for injection solutions have to be sterile and are preferably dispensed into ampoules. Solid carrier substances are e.g. starch, lactose, mannitol, methylcellulose, talcum, highly dispersed silicic acids, higher molecular fatty acids (such as stearic acid), gelatins, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats, solid high-molecular polymers (such as polyethylene glycols); suitable preparations for oral application can optionally also contain flavourings and sweeteners.

The dosage can depend on various factors such as manner of administration, species, age and/or individual state of health. The doses to be administered daily are about 5-

2000 mg/human, preferably 100-500 mg/human and can be taken singly or distributed over several administrations.

Prodrugs of the compounds of the invention are such which are converted in vivo to the pharmacological active compound. The most common prodrugs are carboxylic acid esters, e.g. acetats, ethyl esters etc.

Within the sense of the present invention the following derivatives are preferred in addition to the compounds mentioned in the examples and compounds that can be derived by combining all meanings of substituents mentioned in the claims:

Example 41:

2-ethoxy-10-methoxy-6-methyl-1-pentyloxy-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-9-ol

Example 42:

1,10-dimethoxy-2-hydroxy-6-methyl-3-pentyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-9-ol

Example 43:

1,10-dimethoxy-4-hexyl-2-hydroxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-9-ol

Example 44:

1,2-dihydroxy-3-hexyl-10-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-9-ol

Example 45:

1,10-dimethoxy-3,4-dipentyl-2-hydroxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-9-ol

Example 46:

10-dimethoxy-2-hydroxy-6-methyl-3-pentyl-1-pentyloxy-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-9-ol

Example 47:

1,10-dimethoxy-2-hydroxy-6-methyl-3-octyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-9-ol

Example 48:

1,10-dimethoxy-3-heptyl-2-hydroxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-9-ol

Example 49:

1,10-dimethoxy-2-hydroxy-6-methyl-4-octyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-9-ol

Example 50:

1,10-dimethoxy-4-heptyl-2-hydroxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-9-ol

Example 51:

3,4-dibutyl-1,10-dimethoxy-2-ethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo<de,g>quinoline-9-ol

Example 52

In order to determine the inhibition of MMPs, for example MMP-8, the catalytic domain (isolation and purification see for example Schnierer, S., Kleine, T., Gote, T., Hillemann, A., Knäuper, V., Tschesche, H.,Biochem. Biophys. Res. Commun. (1993) 191, 319-326) is incubated with inhibitors having various concentrations. Subsequently, the initial reaction rate in the conversion of a standard substrate is measured in a manner analogous to Grams F. et al., FEBS 335 (1993) 76-80). Alternatively the percent inhibition will be determined at a distant inhibitor concentration.

The assays for other MMPs are performed in a analogous manner.

Assay buffer: 50 mM Tris/HCl pH 7.6 (Tris= Tris-(hydroxymethyl)-aminomethan) 100 mM NaCl/10 mM $CaCl_2$/5 % MeOH (if necessary)

Enzyme: 8 nM catalytic domain (Met80-Gly242) of human neutrophil collagenase

Substrate: 10 microM DNP-Pro-Leu-Gly-Leu-Trp-Ala-D-Arg-NH2

Total assay volume: 1 ml

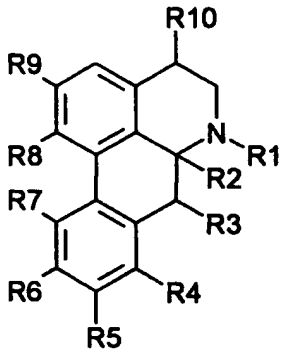
Table 1 shows the inhibition in % at a compound concentration of 100 ng/ml or IC50 values in brackets.

Table 1: Inhibition (%) with different MMPs at 100ng/ml

Compound	Example	MMP 2	MMP 3	MMP 8	MMP 9
Boldin-	12	82%	82%	100% (44 nM)	82%
Glaucine	7	20%	21%	26% (121 nM)	26%
2-*n*-Butyloxy-9-Hydroxy-1-10-dimethoxyaporphine	37	14%	23%	23%	21%

Claims

1. Use of a substatially pure compound of formula I



wherein

R1 represents hydrogen, hydroxy, acyl, halogenyl or C1-C6-alkyl;

R2 represents hydrogen, hydroxy, halogenyl, cyano, C1-C6-alkyl, or acyl;

R3 and R4 represent independently of each other hydrogen, hydroxy, halogenyl, C1-C7-alkyl, acyl or a monocycle;

R5, and R6 represent independently of each other hydrogen, hydroxy, mercapto, C1-C8-alkyl, C1-C7-alkoxy or acyl;

R7 represents hydrogen, hydroxy, halogenyl or amino;

R8 represents hydrogen, hydroxy, mercapto, C1-C8-alkyl, acyl or R8 and R9 represent together O-(CH2)n-O with n equals 1 or 2;

R9 represents hydroxy, mercapto, C1-C7-alkoxy or C1-C7-alkylthio.

R10 represents hydrogen, hydroxy, mercapto, halogenyl or amino, C1-C16-alkyl, acyl, a optionally sustituted mono- or bicyclus;

and pharmacologically acceptable salts or prodrugs thereof,

to produce pharmaceutical agents for the treatment of diseases where MMP activity is envolved.

2. Use as claimed in claim 1 wherein R1 is methyl or hydrogen or R2 is hydrogen or R3 is hydrogen or R4 is hydrogen.

3. Use as claimed in one of the claims 1 or 2 wherein R5 is hydroxy, C1-C3-alkoxy, mercapto, or C1-C3-alkylthio or R6 is C1-C3-alkoxy or R7 is hydroxy or hydrogen.

4. Use as claimed in one of the claims 1 to 3 wherein R8 is hydroxy, C1-C12-alkoxy, mercapto, C1-C12-alkylthio.

5. Use as claimed in one of the claims 1 to 4 wherein R9 is preferrably hydroxy or mercapto.

6. A compound of formula I as given in one of the claims 1 - 5,wherein
R1 represents C2-C5-alkyl or halogenyl;
R2 represents halogenyl, cyano, C2-C5-alkyl, or C2-C5-alkoxy;
R3 represent halogenyl, C1-C7-alkyl or a monocycle
R4 represent halogenyl, C2-C7-alkyl or a monocycle;
R5, R6, R8 and R9 represent independently of each other mercapto, C2-C7-alkyl, C2-C7-alkoxy, or C1-C7-alkylthio;
R7 represents halogenyl or amino;
R10 represents mercapto, halogenyl or amino, C1-C15-alkyl, C1-C15-alkoxy, C1-C15-alkylthio, a optionally sustituted mono- or bicyclus;
and pharmacologically acceptable salts or prodrugs thereof.

7. A compound of formula I as given in one of the claims 1 - 5,
wherein R9 represents mercapto or C1-C7-alkylthio and their pharmacologically acceptable salts, optically active forms thereof or prodrugs thereof.

8. Pharmaceutical composition containing at least one compound of formula I as claimed in one of the claims 6 or 7 in addition to common carrier substances and auxiliary substances.

9. Use of a compound of formula I as claimed in one of the claims 1 to 6 for the production of pharmaceutical agents for treatment of osteo- and rheumatoid arthritis, periodontal diseases, diseases, where the presence of bacteria results in the release of MMPs, corneal ulceration, metastasis, angiogenesis, multiple sclerosis, sun-induced skin-aging, emphysema, restinosis and arteriosclerosis

10. Use of a compound of formula I as claimed in one of the claims 6 or 7 for the production of pharmaceutical agents for treatment of osteo- and rheumatoid arthritis, periodontal diseases, diseases, where the presence of bacteria results in the release of MMPs, corneal ulceration, metastasis, angiogenesis, tumour progression, multiple sclerosis, sun-induced skin-aging, emphysema, and cardiovascular diseases.